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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,107	10/14/1999	PETER KUFER	3816-4000	6846

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,107	KUFER ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,22,28,29,31,32,38,39,42,53-56 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,22,28,29,31,32,38,39,42,53-56 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seq comply letter*.

DETAILED ACTION

1. Claims 1-17, 20-21, 23-27, 30, 33-37, 40-41, 43-52 and 57-64 are cancelled. Claims 18, 22, 32 and 67-68 have been amended.

2. Claims 18-19, 22, 28-29, 31-32, 38-39, 42, 53-56 and 65-68 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

5. The information disclosure statement submitted on 30 June 2002 has been considered by the examiner. However, references Kucherlapati et al, Dermer, Freshney, Gura, Jain and Rudikoff were cited and already considered by the Examiner on the PTO-892 mailed 3/13/2003. Further, since the Office Actions (references C3-C6 and C14-C20) cited on the IDS are not true publications with a publication date, they are not fully in compliance with 37 CFR 1.97 and thus they will not be printed on the face of the patent issuing from this application.

Sequence Requirements

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37

C.F.R. §§ 1.821-1.825. Figures 6-9 contain sequences that are encompassed by the sequences rules and require sequence identifiers (SEQ ID numbers). Applicant is required to either amend the Figures with the corresponding SEQ ID numbers or alternatively applicant may amend the Brief Description of the Figures (beginning at page 17 of the specification) with the corresponding SEQ ID numbers. Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance.

7. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

8. APPLICANT IS GIVEN THE TIME ALLOTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to the undersigned.

Specification

9. The disclosure is objected to because of the following informalities:

a. Applicant is required to update the first line of the specification to indicate that the instant application is a national phase filing of PCT/EP98/02180, filed 4/14/1998.

Applicant is reminded that the priority applications cannot be incorporated by reference after the original filing of the instant application. See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application" (see Part VII).

Applicant is reminded that foreign priority under 35 U.S.C. 119(a-d) does not need to be on the first line of the specification. The examiner acknowledges Applicant's benefit claim to EPO 97106109.8, filed 4/14/1997 presented in the Oath/Declaration is fully compliant with 35 U.S.C. 119(a-d).

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should limit the title to the claimed subject matter, i.e., human antibodies specific for the human 17-1A/EpCAM tumor antigen or similar language.

c. The abstract of the disclosure is objected to because it exceeds 150 words, does not commence on a separate sheet of paper and it contains the legal phraseology "said VH", "said VL", "said receptors" and "said antibody". Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Appropriate correction is required.

Objections/Rejections Withdrawn

10. The rejection of claim 68 under 35 U.S.C. 112, second paragraph as being indefinite is withdrawn in view of the amendments to the claim.

11. The rejection of claims 32 and 56 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing New Matter is withdrawn in view of the amendments to the claims.

12. The rejection of claims 18-19, 28-31, 38-39, 53-55, 65 and 67 under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al in view of Gottlinger et al is withdrawn in view of applicant's arguments.

Response to Arguments

13. The rejection of claims 22, 42 and 68 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained.

The response filed 6/30/2005 has been carefully considered, but is deemed not to be persuasive. The response argues that claims 22 and 42 specify 1 of 3 CDRs for each chain and thus specify 2 of 6 total CDRs. The response states that the methods of the present invention start with a functional 17-1A antibody and it would not require undue experimentation to modify two of the three CDRs of a given chain to obtain antibodies which retain 17-1A binding activity and comprise one fixed or unchanged CDR. In response to these arguments the claims remain broadly drawn to antibodies that comprise only one heavy chain CDR from SEQ ID NO:143 and only one light chain CDR selected from SEQ ID NO:141. Further, with respect to applicant's arguments

pertaining to the method of using a functional 17-1A antibody as a starting point for producing the claimed antibodies, the claims are drawn to the antibody regardless of the method for its production. Thus, the claims broadly encompass taking any one of the three CDRs from the VH chain encoded by SEQ ID NO:143 and selecting any one of the three CDRs from the VL chain encoded by SEQ ID NO:141 and adding four other CDRs from some arbitrary antibody or combinations of CDRs from antibodies of various specificities. For example, the claims encompass taking CDR-H1 encoded by SE ID NO:143 and adding CDR-H2 from an anti-lysozyme antibody and perhaps a CDR-H3 from an anti-CEA antibody and then pairing that with any one of the three CDRs encoded by SEQ ID NO:141 and selecting two other CDRs from just any other antibody, wherein the antibody binds the human 17-1A tumor antigen. One of skill in the art would neither predict nor expect the appropriate functioning of the antibody as broadly as claimed. Applicant has not provided any guidance or direction to assist the skilled artisan in selecting a starting point (i.e., which heavy and light chain CDR are selected from SEQ ID Nos:143 and 141), or provided guidance as to which other CDRs are to be paired with the selected heavy and light chain CDR from SEQ ID Nos:143 and 141 wherein the resulting antibody has the required 17-1A antigen binding function. The evidence of Rudikoff et al indicates that such an endeavor would be unpredictable, as even minor changes in a single CDR may result in loss of antigen-binding function. The written disclosure of the present application only provides guidance for antibodies comprising all three heavy chain CDRs encoded by SEQ ID NO:143 and all three light chain CDRs encoded by SEQ ID NO:141 that bind the 17-1A human tumor antigen.

Amending the claims to recite that the claimed antibodies comprise all three VH CDRs encoded by SEQ ID NO:143 and all three VL CDRs of SEQ ID NO:141, preferably indicating the particular nucleotide residues which define these CDRs (see Fig legend for Figs 6 and 7) would overcome this rejection.

New Grounds of Rejections

14. Claims 22, 32, 42, 65 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 22, 42 and 68 are indefinite in the recitation of "CDR-encoding portion" in claim 22 and "CDR-encoding segments" in claim 68. Does the phrase mean that at least one CDR is encoded by the recited nucleotide sequence or is just a portion or just a segment of a CDR encoded by the recited sequences? As written, the metes and bounds of the claims cannot be determined. Amending the claims to recite the particular nucleotide residues of the CDR contemplated by the claim would overcome this rejection.

b. Claim 65 is indefinite in the recitation "further comprising, fused to said human VH and VL chains, (a) the same or other VH or VL chains". It is unclear what is contemplated by the phrase because the structure of the claimed antibody molecule is ambiguous. Do the human VH and human VL chains that bind the 17-1A antigen as required by the base claim further comprise a human VH chain that binds to 17-1A (i.e., "the same...VH") or some other VH chain that binds a different antigen (i.e., "other VH")

and the nature of the fusion is also ambiguous. Do the human VH and human VL that bind the 17-1A antigen further comprise a fused VH chain such that the antibody molecule is VH-VH-VL or VH-VL-VH or are multiple same or other VH chains fused? Similar ambiguities exist with respect to the fused same or other VL chains. One of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

c. Claims 22, 68 recites the limitations "said VH chain" and "said VL chain". There is insufficient antecedent basis for these limitations in the claim. It is unclear if the recited VH chain and VL chain are the human VH and human VL chain, particularly in view of the recitation that the antibody further comprises "the same or other VH or VL chains", which may or may not be human VH and VL chains.

d. Claim 32 recites the limitation "the VH chain" and "the VL chain". There is insufficient antecedent basis for these limitations in the claim. Base claim 28 recites that the VH and VL chains are human VH and VL chains.

15. Claim 65 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human antibody or human antigen-binding fragment thereof comprising the CDRs of SEQ ID Nos:143 and 141 and binds the 17-1A human tumor antigen, does not reasonably provide enablement for method of producing a human antibody or human antigen-binding fragment thereof comprising the human VH and VL chains that bind the 17-1A antigen and further comprising the same or other VH or VL chains, which encompasses VH-VH and VL-VL pairs as well as VH-VH-VL and

VH-VL-VH antibodies that do not bind antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claim is drawn to a method of producing an antibody or antibody fragment comprising the human VH and VL chains that bind the 17-1A antigen and further comprising the same or other VH or VL chains, which broadly encompasses VH-VH and VL-VL pairs as well as VH-VH-VL and VH-VL-VH antibodies, which do not contain three CDRs from the heavy chain and three CDRs from the light chain and do not bind antigen.

The specification discloses only antibodies that contain both a human VH and a human VL chain and the antibodies bind the 17-1A human tumor antigen (see examples). The specification does not enable antibodies comprising VH-VH or VL-VL pairs that do not contain three CDRs from the heavy chain and three CDRs from the light chain and do not bind antigen.

The claims encompass methods of producing an antibody or antibody fragment comprising VH-VH or VL-VL pairs, which do not contain complementary CDRs from a VH chain and a VL chain and do not bind antigen. It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79:1979-1983, cited previously on PTO-892 mailed 3/13/2003). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that an

antibody or antibody fragment comprising a VH-VH or VL-VL pair, which do not consist of a full complement of heavy and light chain CDRs, would form a functional antigen binding site and have the required antigen-binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing an antibody or antibody fragment comprising a VH-VH or VL-VL pair resulting in an antibody or antibody fragment that binds antigen. The specification provides no direction or guidance regarding how to use the antibodies as broadly defined by the claim.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to the presently claimed method of producing a human antibody and antigen-binding fragments thereof. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

16. Claims 18-19, 28-29, 31, 38-39, 53-55 and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al (U.S. Patent 5,885,793, 102(e) date 10/94, previously cited on PTO-892 mailed 3/13/2003) in view of Gottlinger et al (International Journal of Cancer 38(1):47-53, 1986, Ids reference filed 10/14/1999).

The claims are drawn to a an antibody or an antibody fragment comprising a human VH chain is from unprimed mature human B-lymphocytes and said VL chain is from a naturally occurring human B cell repertoire, wherein the antibody is low or not

immunogenic in human and recognizes an epitope of the extracellular domain of the 17-1A antigen and wherein the antibody is fused to heavy and light chain constant regions, that may be from human IgG1 or human IgG3 and the antibody may further comprise a non-proteinaceous pharmaceutical or biologically active molecule linked to said human VH and VL chains. Further, the claims are drawn to pharmaceutical compositions comprising said antibody and a pharmaceutically acceptable carrier.

Griffiths et al teach anti-self antibodies and antigen-binding fragments (i.e., Fab, F(ab)2, scFv, Fv, dAb and Fd fragments) and Griffiths teaches that primers specific for B cell surface IgD may be particularly suitable for isolation of anti-self antibodies and will produce a repertoire of antibody genes enriched for the naïve, unselected genes encoding V domains (see column 9, lines 15-31, column 15, lines 41-44, column 18, lines 39-40). Griffiths et al also teach that a rich source of anti-self antibodies is V gene sequences prepared by synthetic recombination of V, D and J segments and the use of germline V genes is valuable for the isolation of anti-self antibodies because B lymphocytes directed against self antigens are functionally silenced and those directed against multivalent self antigens are eliminated (see column 9). Griffiths et al teach that the antibodies may be linked to an Fc region for mediating cell killing using the natural effector function or may be linked to other markers such as enzymes, fluoresceins (biologically active molecule) or radioisotopes (non-proteinous pharmaceutical) for diagnostic in vivo imaging (see column 20, lines 47-57, column 13, lines 42-48, column 6, lines 49-52). Griffiths et al also teach the anti-self antibodies as a therapeutic or prophylactic medicament or diagnostic product and one of skill in the art would

reasonably envisage such a composition as comprising the anti-self antibody and a pharmaceutically acceptable carrier. Griffiths et al does not specifically teach an antibody that binds the human 17-1A antigen expressed on the surface of tumor cells. This deficiency is made up for in the teachings of Gottlinger et al.

Gottlinger et al teach the human 17-1A antigen expressed on human colorectal carcinomas and antibodies directed to the antigen (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a human anti-self antibody against the 17-1A human tumor antigen of Gottlinger et al by the method of Griffiths et al for diagnosis and therapy of human colorectal carcinomas.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a human anti-self antibody against the 17-1A human tumor antigen of Gottlinger et al by the method of Griffiths et al for diagnosis and therapy of human colorectal carcinomas because Griffiths et al teach that it is difficult to produce antibodies which recognize human self antigens due to tolerance (see column 6, lines 17-20 and column 1, lines 24-27) and Griffiths teaches that primers specific for human B cell surface IgD are particularly suitable for isolation of anti-self antibodies and will produce a repertoire of antibody genes enriched for the naïve, unselected genes encoding V domains, and Gottlinger et al teach the 17-1A human tumor antigen expressed on human colorectal carcinomas and "human anti-self antibodies are of particular value for in vivo therapeutic and diagnostic purposes, since they avoid the problems arising from antigenicity of foreign, e.g., mouse antibodies"

(column 1, lines 13-16). Therefore, one of ordinary skill in the art would have been motivated at the time the invention was made to have produced low or non-immunogenic human antibodies against the human self antigen 17-1A of Gottlinger et al according to the teachings of Griffiths et al, using primers specific for human B cell surface IgD, which unlike surface IgM, IgD surface expression remains unchanged upon exposure to self and hence, primers specific for surface IgD are particularly suitable for producing anti-self antibodies, thereby overcoming the difficulties associated with obtaining antibodies which recognize human self antigens due to tolerance and antibodies raised against the human 17-1A tumor antigen were effective immunotherapeutic agents against colorectal carcinomas according to Gottlinger et al (see page 47, left column). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a human anti-self antibody against the 17-1A human tumor antigen wherein the V domains of the antibody are derived from human B cell surface IgD (i.e., unprimed mature human B lymphocytes/ naturally occurring human B cell repertoire) for diagnosis and therapy of human colorectal carcinomas in view of Griffiths et al and Gottlinger et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to Tony Parks for Art Unit 1643 whose telephone number is 571-272-0543.

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Application No. 09/403,107

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE